

TITLE: PDL-1 inhibition with Avelumab and concurrent second-generation ADT in African Americans with castrate-resistant metastatic prostate cancer.

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1. TRIAL SUMMARY

Abbreviated Title	Phase II Trial of Avelumab plus 2 nd -generation ADT in AA Subjects with mCRPC
Sponsor Product Identifiers	Avelumab
Trial Phase	Phase II
Clinical Indication	Metastatic Castration-Resistant Prostate Cancer (mCRPC)
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	Avelumab 10mg/kg every 2 weeks (Q2W) + 2 nd generation ADT
Number of trial subjects	Thirteen subjects will be enrolled in initial cohort with a potential for expansion to a total of 27AA patients
Estimated time to enrollment	The trial will require approximately 40 months to enrollment for initial cohort from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.

Duration of Participation	<p>Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specified contact.</p> <p>After a screening phase of 21 days (with 28 days for imaging), eligible subjects will be enrolled into an initial cohort. Subjects will receive avelumab and continue with 2nd-generation ADT they had been already receiving.</p> <p>Treatment will continue until documented disease progression, unacceptable adverse events (AEs), intercurrent illness that prevents further administration of treatment, Investigator's decision to withdraw the subject, subject withdrawal of consent, noncompliance with trial treatment or procedure requirements, subject receives 52 administrations of avelumab (approximately 2 years), or administrative reasons requiring the cessation of treatment. Treatment may continue beyond progression in cases where the treating physician determines that clinical benefit is occurring.</p> <p>Subjects who discontinue for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression, initiation of a non-study prostate cancer treatment, withdrawal of consent, or becoming lost to follow-up. All subjects will be followed by telephone for overall survival until death, withdrawal of consent, or study closure.</p>
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1.1 TRIAL DESIGN

This is a nonrandomized, open-label trial of avelumab in subjects with metastatic castration-resistant prostate cancer (mCRPC) experiencing PSA or radiographic progression while receiving 2nd generation ADT (abiraterone / enzalutamide/ apalutamide or darolutamide). Metastases must be radiographically evident by whole body bone scintigraphy or CT/MRI scan.

Progression of disease at time of enrollment will be defined as either

1. PSA progression will be defined by PSA rise on 2 consecutive measurements at least 1 week apart with baseline PSA of $\geq 2\text{ng/dL}$.
2. And/or radiographic disease progression in soft tissue or bone with or without PSA progression

Thirteen African American subjects will be enrolled into the initial cohort.

If at least one positive response (PSA decrease by $\geq 50\%$ and or radiographic per RECIST 1.1) is found, the study will be expanded to accrue a total of 27 patients. The trial will be conducted in accordance with Good Clinical Practices.

Subjects enrolled in the study will receive avelumab 10 mg/kg every 2 weeks (Q2W) and continue their previously started 2nd generation ADT (abiraterone or enzalutamide).

All subjects will undergo radiographic imaging assessments and PSA assessments to evaluate response to treatment at regular intervals. On study imaging will be assessed every 12 weeks. Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 will be adapted per the consensus guidelines of the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) as described in Appendix A/B to account for the tumor progression patterns seen in bone metastases in prostate cancer. PSA will be obtained every 2 weeks with PSA progression assessed per PCWG3.

Adverse events (AEs) will be monitored throughout the trial and graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (see Appendix C).

Treatment with avelumab will continue until documented confirmed disease progression, unacceptable AEs, intercurrent illness that prevents further administration of treatment, Investigator's decision to withdraw the subject, subject discontinuation from the study, noncompliance with trial treatment or procedure requirements, subject receives 52 administrations of avelumab (approximately 2 years), or administrative reasons requiring the cessation of treatment.

After the end of treatment, each subject will be followed for 30 days for AE monitoring (serious AEs will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier). Subjects who discontinue treatment for reasons other than disease progression will remain on study and continue to undergo study-related disease assessments until documented disease progression, initiation of a new non-study prostate cancer treatment, withdrawal of consent, or becoming lost to follow-up. All subjects will enter survival follow up, and will be contacted at their regularly scheduled clinic visit, or by telephone approximately every 6 months, until death or withdrawal of consent or end of study.

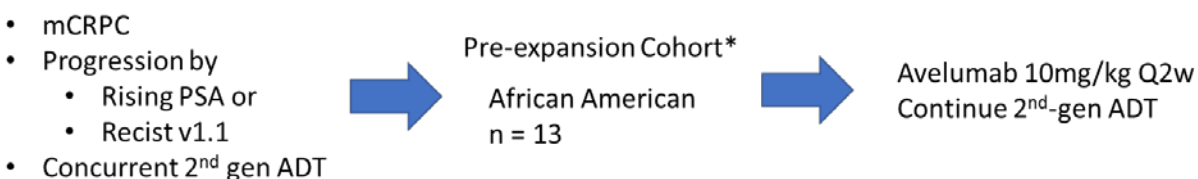
Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 7.0.

1.2 TRIAL DIAGRAM

African American subjects with mCRPC currently receiving either abiraterone or enzalutamide and documented PSA progression (on serial PSA's at least 1 week apart) and/or worsening radiographic disease by Prostate Cancer Clinical Trials Working Group 3 (PCWG3) will enroll into the pre-expansion Cohort.

The trial design is depicted in Figure 1.

Figure 1.



*Cohort will be expanded to 27 if ≥ 1 response via PCWG3 seen in the first 13 patients accrued.

2.0 BACKGROUND AND RATIONALE

PD-1 Inhibitors and Prostate Cancer

PD-1 inhibitors have garnered considerable interest and activity in a variety of advanced cancers. Prostate cancer, as well as colon cancer, were initially considered to be an exception to this rule. Graff et al. (1) have recently publicized data demonstrating considerable effect of pembrolizumab in a subset of men with advanced CRPC. This data is revitalizing the field of PD-1 inhibition in prostate cancer. Direct personal communication with Dr. Graff (November 2016) indicates that analysis of the tumor specimens is not yet complete but in at least one case, there is an underlying micro-satellite instability (MSI) suggesting the possibility of an underlying mismatch repair defect among some responders.

Careful studies of mismatch repair defects indicate that in colon cancer individuals whose tumors have these mismatch repair defects can markedly benefit from PD1 inhibition (2). Merck in fact has now received FDA approval of pembrolizumab in MSI cancers (3).

Mismatch and DNA Repair Issues in Prostate Cancer

Studies in Lynch Syndrome and prostate cancer indicate mismatch repair alterations can clearly occur in prostate cancer (4,5). Some data suggest that Lynch syndrome patients have a higher risk of prostate cancer (5). In one study, 488 Lynch syndrome families with disease-predisposing germline mutations in MLH1, MSH2, MSH6 or PMS2 were identified in the national Danish registry. In this cohort of 1609 males (677 mutation carriers and 932 first-degree relatives), prostate cancer developed in 16 mutation carriers and in 12 first-degree relatives. The tumors were linked to disease-predisposing mutations in MSH2 (n=14), MLH1 (n=8) and MSH6 (n= 6). We note that the effects of PD1 inhibition in men DNA repair mutations are not yet defined but we believe this issue is of potential significance.

In the large studies on inherited (germline) DNA in metastatic CRPC published by Pritchard et al (6) in 692 patients, mutations in DNA mismatch were detected as follows: MLH1 (n=0), PMS2 (n=2), MSH2 (n=1), and MSH6 (n=1). None of these frequencies were distinct from the large control population. On the other hand, a variety of DNA repair mutations including: BRCA2 (n=37), BRCA1 (n=6), ATM (n=11), GEN1 (n=2), RAD51D (n=3), CHEK2 (n=10) and PALB2 (n=3) germline mutations were more common in CRPC patients as compared to controls. Notably this study used exomic sequencing and thus incomplete data are available from this data set.

A distinct autopsy study by Pritchard et al (7), demonstrated 12% (7 of 60) of advanced prostate cancers were hypermutated, and all of the hypermutated cancers had mismatch repair gene mutations and MSI. Quite interestingly, mutations were typically complex MSH2 or MSH6 structural rearrangements rather than epigenetic MLH1 silencing. These assays for MSH2 and MSH6 alterations involved a targeted deep sequencing approach (BROCA assay) that included capture of both intronic and flanking DNA sequences in addition to exons.

There are current collaborations between Tulane University and the Pritchard group studying mismatch repair and DNA repair genes in men of African-American ancestry but results are not yet available. We anticipate that this would be part of the correlative studies going forward with immune modulation.

Race Differences

The relationship between prostate cancer and race has been well studied and unequivocal data demonstrate African-American (AA) men are at higher risk for prostate cancer death as compared to other ethnic groups in the United States. In addition to having higher incidence of death, there's an earlier onset of disease; considerable work has been ongoing to understand why these disparities exist.

Provocative findings demonstrate prostate cancer to be an immune-mediated treatment responsive disease. In solid tumors, the very first immune mediated treatment to prolong overall survival (OS) in men with metastatic castrate resistant prostate cancer (CRPC) occurred after treatments with sipuleucel-T (8). Though the overall effects were modest, and the therapy expensive, the phase III IMPACT trial was pivotal for FDA approval and this agent is now used in the United States for CRPC therapy.

While not much has been yet publicized, the effects of this immune-based therapy appear to be more pronounced in AA men as compared to Caucasian men. In an analysis of all randomized trials with sipuleucel-T, the hazard ratio of OS in AA men was a remarkable 0.288 [95% CI: 0.125, 0.662]; $p = .003$ (9). AA men treated with this therapy had median overall survival benefit of 45.3 months versus 14.6 months in the control arm, a median survival difference of 30.7 months.

More recent data from a much larger study submitted with sipuleucel-T (10) confirm and extend the sipuleucel-T initial findings with a larger matched cohort. AA pts had a significantly longer median OS of 39.5 months vs 28.1 months for CAU pts ($p < 0.001$; HR 0.665, 95% CI 0.530-0.835). After univariate and multivariate analyses, six baseline characteristics were significantly associated with OS - including AA men.

3.0 PATIENT POPULATION

African-American men with histologically or cytologically confirmed adenocarcinoma of the prostate, currently undergoing treatment for castrate-resistant metastatic disease with a second-generation androgen deprivation therapy (abiraterone/enzalutamide/apalutamide or darolutamide).

4.0 HYPOTHESIS

We hypothesize African-American men are responsive to inhibition of the PD-1 signaling pathway and propose to test this concept in a pilot clinical trial. We also propose to link these therapeutic responses with correlative studies on mismatch and DNA repair alterations using the BROCA assays.

5.0 ENDPOINTS

5.1 Primary: to evaluate the proportion of men with PSA response $\geq 50\%$

5.2 Secondary: to assess PSA progression-free survival (PFS); radiographic PFS, RECISTv1.1 response, overall survival (OS), and safety

5.3 Ancillary studies

5.3.1 To establish the relationships between DNA based biomarkers and clinical activity

5.3.2 Mismatch repair and DNA repair assays on germline and where feasible somatic samples using BROCA assays that extend beyond the exomic sequencing typically used.

6.0 METHODS

6.1 Entry Criteria

Diagnosis/Condition for entry into trial: Male subjects at least 18 years of age with mCRPC whom are currently receiving treatment with second-generation androgen deprivation therapy (abiraterone/enzalutamide/apalutimide/darolutamide) with evidence of progression of disease. Patients receiving a second-generation androgen deprivation therapy (2nd generation ADT) for metastatic hormone sensitive prostate cancer (mHSPC), who show evidence of progression to mCRPC, will be allowed to participate in this study.

6.2 Subject Inclusion Criteria

To be eligible for participation in this trial, the subject must:

- 1 Must be of African descent; **Black or African American:** A person having origins in any of the black racial groups of Africa. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American.”
- 2 Be willing and able to provide written informed consent for the trial.
- 3 Be ≥ 18 years of age on day of signing informed consent.
- 4 Have histologically or cytologically confirmed adenocarcinoma of the prostate without small cell histology. Diagnosis must be stated in a pathology report.
- 5 Have evidence of metastatic disease as determined by CT/MRI scans and/or bone metastases by whole body bone scintigraphy. (Use MRI if CT is contraindicated, and for imaging of the brain if clinically indicated).
- 6 Have documented disease progression within 3 months of screening, as determined by the Investigator, by means of at least one of the following:
 - PSA progression as defined by a minimum of two rising PSA levels with an interval of ≥ 1 week between each assessment where the PSA value at screening should be ≥ 2 ng/mL.
 - Radiographic disease progression in soft tissue or bone with or without PSA progression as determined by Recist 1.1 and/or PCWG3
- 7 Have ongoing androgen deprivation with serum testosterone < 50 ng/dL (< 2.0 nM). If the subject is currently being treated with LHRH agonists or antagonists (for subjects who have not undergone an orchiectomy). This treatment must be continued throughout the study.
- 8 Be receiving and tolerating either abiraterone acetate, enzalutamide, apalutamide or darolutamide for at least 8 weeks prior to documented disease progression. Note: the 2nd generation ADT that the patient is currently progression on needs to be the first 2nd gen ADT used in the CRPC setting
- 9 Have a performance status of 0, 1 or 2 on the Eastern Cooperative Oncology Group

(ECOG) Performance Scale (Appendix D).

- 10 Male subjects of reproductive potential must agree practice abstinence from heterosexual activity OR use a highly effective method of contraception, starting at the time of informed consent and continue through 60 days after the last dose of study therapy (see section 6.1.1.)
- 11 Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 10 days of treatment initiation.

Table 1. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	$>1,500 \times 10^9/L$
Platelets	$\geq 100,000 \times 10^9/L$
Hemoglobin ^a	$\geq 9 \text{ g/dL}$
Renal	
Creatinine OR	$<1.5 \text{ X ULN}$ OR
Measured or calculated ^b creatinine clearance (GRF can also be used in place of creatinine or creatinine clearance)	$\geq 30.0 \text{ mL/min}$ for subject with creatinine levels $> 2\text{X}$ institutional ULN
Hepatic	
Serum Total Bilirubin	$\leq 1.5 \text{ X ULN}$ (unless patient has Gilbert's syndrome)
AST (SGOT) and ALT (SGPT)	$\leq 2.5 \text{ X ULN}$ OR $\leq 5\text{xULN}$ for subjects with liver metastases
a. Hemoglobin may reach threshold by transfusion b. Creatinine clearance should be calculated according to the Cockcroft-Gault formula or per institutional standard.	

6.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

- 1 Is currently participating and receiving study therapy in a clinical trial, or has participated in a study of an investigational agent (and received study therapy or used an investigation device) within 4 weeks of the first dose of study treatment.
- 2 No more than one line of a 2nd generation ADT (abiraterone acetate /enzalutamide/ apalutamide/darolutamide) for mCRPC is permitted for study entry.
- 3 Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

Note: the following are allowed: a. intranasal, inhaled, topical steroids, or local steroid injection (e.g., intraarticular injection); b. systemic corticosteroids at physiological doses \leq 10mg/day of prednisone or equivalent; c. steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).

- 4 Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to the first dose of trial treatment or who has not recovered (i.e., \leq Grade 1 or at baseline) from adverse events due to mAbs administered more than 4 weeks earlier.
- 5 Has had >2 prior systemic chemotherapy agents for mCRPC Note: chemotherapy in the mHSPC setting is allowed
- 6 Prior surgery within 4 weeks of initiating study treatment
Note: If subjects received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to the first dose of trial treatment.
- 7 Has any additional malignancy that has required active treatment in the last 3 years.
Exceptions include: basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or low-grade Ta or T1 urothelial carcinoma of that bladder that has undergone potentially curative therapy.
- 8 Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis.
Note: Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
- 9 Has an active autoimmune disease that might deteriorate when receiving an immune-stimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible.
- 10 Has had prior organ transplantation including allogenic stem-cell transplantation.
- 11 Has an active infection requiring systemic therapy.
- 12 Has active, clinically significant Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies). Patients with well controlled HIV will be allowed to be enrolled into the study.
- 13 Has Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test is positive).
- 14 Has received a live vaccine within 4 weeks of first dose of avelumab; live vaccines are prohibited throughout course of the trial. Inactivated vaccines are allowed.

- 15 Has known prior severe hypersensitivity to investigational product or component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v4.3 Grade ≥ 3).
- 16 Has clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6months prior to enrollment), myocardial infarction (< 6months prior to enrollment), unstable angina, congestive heart failure (\geq New York Heart Association Classification Class II), or serious cardiac ventricular arrhythmia requiring medication.
- 17 Persisting toxicity related to prior therapy (NCI CTCAE v. 4.3 Grade > 1); however, alopecia, sensory neuropathy Grade ≤ 2 , or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable.
- 18 Other severe acute or chronic medical conditions including colitis, inflammatory bowel disease, immune pneumonitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

6.4 Trial Treatment(s)

6.4.1 Experimental treatment to be used in this trial:

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
avelumab	10 mg/kg	Q2W	IV infusion	Day 1 of each cycle	Experimental

Trial treatment should begin on the day 1 of cycle 1

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

6.4.2 Non-experimental treatments shall be one of the following:

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Abiraterone	1000 mg	Daily	PO on empty stomach	Daily	Standard of care

Enzalutamide	160 mg	Daily	PO	Daily	Standard of care
Darolutimide	600 mg	BID	PO	Daily	Standard of care
Apalutamide	240 mg	Daily	PO	Daily	Standard of care

Patients with dose modifications made prior to study entry may be maintained (at lower dose) as clinically indicated

6.5 Dose Modification

There are no dose modifications allowed for the study drug Avelumab.

Dose modifications for non-experimental treatments will be allowed per clinical discretion.

Adverse events (both non-serious and serious) associated with avelumab exposure may represent an immunological etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Avelumab should be withheld for drug-related toxicities and severe life-threatening AEs as per Tables 2 and 3.

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, subject vacation, and/or holidays). Subjects should be placed back on study therapy within 4 weeks of the scheduled interruption, unless otherwise discussed with the managing provider. The reason for interruption should be documented in the subject's study record. See below for suggested management of potential adverse reactions:

Table 2. Management of Immune-mediated Adverse Reactions

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v4)	Initial Management	Follow-up Management
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (e.g. loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2, 3 or 4.

Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Withhold avelumab therapy Symptomatic treatment	If improves to Grade ≤ 1 : Resume avelumab therapy If persists > 5-7 days or recurs: Treat as Grade 3 or 4.
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 h; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade ≤ 1 , then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3). If worsens, persists > 3 to 5 days, or recurs after improvement: Add infliximab 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.
Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4)	Initial Management	Follow-up Management
Grade 1 to 2 Covering $\leq 30\%$ body surface area	Continue avelumab therapy Symptomatic therapy (for example, antihistamines, topical steroids)	If persists > 1 to 2 weeks or recurs: Withhold avelumab therapy Consider skin biopsy Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Covering > 30% body surface area; Grade 4: Life threatening consequences	Withhold avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3. Consider skin biopsy Dermatology consult	If improves to Grade ≤ 1 : Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).

	1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4)	Initial Management	Follow-up Management
Grade 1 Radiographic changes only	Consider withholding avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-assess at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms	Withhold avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily; consider hospitalization 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	Re-assess every 1 to 3 days If improves: When symptoms return to Grade ≤ 1 , taper steroids over at least 1 month, and then resume avelumab therapy following steroids taper If not improving after 2 weeks or worsening: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening	Permanently discontinue avelumab therapy. Hospitalize. Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade ≤ 1 : Taper steroids over at least 1 month If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4)	Initial Management	Follow-up Management

Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN to 1.5 x ULN	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4.
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days.	If returns to Grade ≤ 1: Resume routine monitoring; resume avelumab therapy. If elevation persists > 5 to 7 days or worsens: Treat as Grade 3 to 4.
Grade 3 to 4 AST or ALT > 5 x ULN and/or total bilirubin > 3 x ULN	Permanently discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade ≤ 1: Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.
Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4)	Initial Management	Follow-up Management
Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue avelumab therapy	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Grade ≤ 1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue avelumab therapy Monitor creatinine daily	If returns to Grade ≤ 1: Taper steroids over at least 1 month.

	1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	
Cardiac irAEs		
Myocarditis	Initial Management	Follow-up Management
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold avelumab therapy. Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A).
<p>*Local guidelines, or e.g. ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001</p>		
Endocrine irAEs		
Endocrine Disorder	Initial Management	Follow-up Management
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue avelumab therapy Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.

	adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold avelumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH): <ul style="list-style-type: none"> • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated If hypophysitis confirmed: <ul style="list-style-type: none"> • Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month • Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider 	Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate.

	<p>hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month.</p> <ul style="list-style-type: none"> Add prophylactic antibiotics for opportunistic infections. 	
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4)	Initial Management	Follow-up Management
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation	<p>If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy</p> <p>If irAE is confirmed, treat as Grade 2 or 3 irAE.</p>
Grade 2 irAE or first occurrence of Grade 3 irAE	<p>Withhold avelumab therapy</p> <p>1.0 to 2.0 mg/kg/day prednisone or equivalent</p> <p>Add prophylactic antibiotics for opportunistic infections</p> <p>Specialty consult as appropriate</p>	<p>If improves to Grade \leq 1:</p> <p>Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.</p>
Recurrence of same Grade 3 irAEs	<p>Permanently discontinue avelumab therapy</p> <p>1.0 to 2.0 mg/kg/day prednisone or equivalent</p> <p>Add prophylactic antibiotics for opportunistic infections</p> <p>Specialty consult as appropriate</p>	<p>If improves to Grade \leq 1:</p> <p>Taper steroids over at least 1 month.</p>
Grade 4	<p>Permanently discontinue avelumab therapy</p> <p>1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed</p> <p>Add prophylactic antibiotics for opportunistic infections</p> <p>Specialty consult.</p>	<p>If improves to Grade \leq 1:</p> <p>Taper steroids over at least 1 month</p>
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12	<p>Permanently discontinue avelumab therapy</p> <p>Specialty consult</p>	

<p>weeks for reasons other than hormonal replacement for adrenal insufficiency</p> <p>Persistent Grade 2 or 3 irAE lasting 12 weeks or longer</p>		
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Abbreviations: ACTH=adrenocorticotrophic hormone; ADL=activities of daily living; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BNP=B-type natriuretic peptide; CK-MB=creatinine kinase MB; CT= computed tomography; FSH=follicle-stimulating hormone; GH=growth hormone; IGF-1=insulin-like growth factor 1; irAE=immune related adverse event; IV=intravenous; LH=luteinizing hormone; MRI=magnetic resonance imaging; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PRL=prolactin; T4=thyroxine; TSH=thyroid stimulating hormone; ULN=upper limit of normal.

6.6 Timing of Administration

The first infusion should be administered within 21 days of screening. Avelumab should be administered on Day 1 of each 2 week cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 7).

6.7 Concomitant Medications/Vaccinations

6.7.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF. Subject may remain on anti-coagulation therapy as long as the PT or PTT is within therapeutic range of the intended use of anticoagulants.

6.7.2 Prohibited Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required.

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biologic therapy
- GM-CSF

- Immunotherapy not specified in this protocol
- Investigational agents other than avelumab
- Any other second-generation androgen deprivation therapy other than the one the patient was enrolled into the trial on (patients cannot switch between non-experimental therapies).
- Systemic radiotherapy
 - Note: Palliative localized radiation therapy to a site of pre-existing disease may be permitted while on study. The radiation treatment field may not include a target or measurable lesion by RECIST 1.1. (see section 6.10)
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, rabies, Bacillus Calmette-Guerin (BCG), and oral typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g., FluMist[®]) are live attenuated vaccines, and are not allowed.

6.8 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator.

6.9 Infusion Reaction Treatment Guidelines

Table 3. Treatment Modification for Symptoms of Infusion-Related Reactions

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the avelumab infusion rate by 50% and monitor closely for any worsening.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h.	Temporarily discontinue avelumab infusion. Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop avelumab infusion immediately and disconnect infusion tubing from the subject. Subjects must be withdrawn immediately from study avelumab and must not receive any further avelumab treatment.
- If avelumab infusion rate has been decreased by 50% or interrupted due to an infusion reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction is observed in the next scheduled infusion, the infusion rate may be returned to baseline at the subsequent infusions based on investigator's medical judgment. - If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice.	

IV = intravenous; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatory drugs.

6.10 Radiotherapy/Surgical Intervention

The use of radiotherapy or surgical intervention while on study must be recorded in the trial database.

Localized palliative radiation therapy to any site of disease may be permitted while on study. Patients may continue treatment on study beyond (investigator's assessed RECIST v1.1 or PCWG3 defined) progression if patient is tolerating therapy and exhibiting investigator-assessed clinical benefit (11).

Use of surgical intervention should be completed as medically necessary. Continuation of treatment on study after a surgical intervention needs to be cleared by the Principle Investigator.

6.11 Diet/Activity/Contraception

6.11.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

6.11.2 Contraception

Avelumab may have adverse effects on a fetus in utero. Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. To participate in the study, subjects of childbearing potential must adhere to the contraception requirement from the time of informed consent throughout the study period up to 60 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study. If a patient's partner does become pregnant, the patient needs to inform the Principle Investigator immediately.

For this trial, male subjects will be considered of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Male subjects of reproductive potential must agree to avoid impregnating a partner while receiving study drug and for 30 days after the last dose of study drug by complying with one of the following:

- 1) practice abstinence† from heterosexual activity;
OR
- 2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection.

† Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡ If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region

6.12 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward incident occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 8.

In this trial, a subject may discontinue from treatment but continue to participate in the regularly scheduled activities, as long as the subject does not withdraw consent.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- The subject is lost to follow-up.

A subject must be discontinued from treatment but should continue to be monitored in the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) discontinues treatment but agrees to continue to participate in the regularly scheduled study activities.

Documented disease progression as assessed by the investigator using RECIST 1.1 guidelines or for bone disease use PCWG3 criteria (Appendix B). (Clinical deterioration will not be considered progression).

- Intercurrent illness that prevents further administration of treatment.
- Noncompliance with trial treatment or procedure requirements.
- Administrative reasons.

The End of Treatment and Follow-up visit procedures are listed in Section 7.0 (Trial Flow Chart). After the end of treatment, each subject will be followed for 30 days for AE monitoring (SAEs will be collected for 90 days after the last dose of treatment).

Subjects who discontinue for reasons other than PD will have post-treatment follow-up for disease status until disease progression, initiation of a non-study prostate cancer treatment, withdrawal of consent or loss to follow-up.

After documented disease progression or the start of new antineoplastic therapy, each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.13 Safety Monitoring

6.13.1 Safety relevant inclusion and exclusion criteria: (see Table 1)

Minimum required safety-related inclusion and exclusion criteria for avelumab to be included in the study protocols are described in Table 1. Additional inclusion and exclusion criteria should be considered based on requirements related to other drugs used in combination treatments, target population or study objectives as well as based on Sponsor (investigator) judgment.

6.13.2 Safety assessments

- Blood chemistry and hematology assessments: must be performed at baseline, prior to each avelumab dose, at end of treatment visit and at 30 days post-treatment safety follow-up.
- Free T4 and TSH must be performed at baseline and at least every 8 weeks during treatment and at end of treatment or 30 days post-treatment safety follow-up (if not performed in the previous 8 weeks).

6.13.3 Extended safety follow-up

- Given the potential risk for delayed immune-related toxicities, safety follow-up for SAEs must be performed up to 90 days after the last dose of avelumab administration.
- The extended safety follow-up beyond 30 days after last avelumab administration may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call.

6.13.4 Special Precautions for Administration

- Premedication: In order to mitigate infusion-related reactions, a premedication with an antihistamine and with paracetamol (acetaminophen) 30 to 60 minutes prior to the first 4 infusions of avelumab is mandatory (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol IV or oral). Premedication should be administered for subsequent avelumab infusions based upon clinical judgment and presence/severity of prior infusion reactions. This may be modified based on local treatment standards and guidelines, as appropriate.
- Setting: Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

- Observation period: Following avelumab infusions, patients must be observed for 30 minutes post-infusion for potential infusion-related reactions for the first four doses.

6.14 Toxicity Management (see Table 2 and Table 3):

Treatment Modification for Symptoms of Infusion-Related Reactions (Table 2)

Management of immune-mediated adverse reactions (Table 3)

6.15 Safety Reporting

The Sponsor-Investigator is responsible for safety reporting and to identify and follow-up on Serious Adverse Events (SAEs) experienced by participants in the study and to forward the information to the local regulatory authorities and EMD Serono, as required by local regulations (for regulatory reporting) and as required by the ISS agreement (for reporting to EMD Serono).

Additional site(s) will report directly to Tulane Cancer Center Office of Clinical Research who will forward to the regulatory authorities and EMD Serono as necessary.

The following reportable events must be submitted to EMD Serono within 2 business days or 3 calendar days (whichever comes first) using the applicable safety report form provided. The Sponsor-Investigator Dr. Jodi Layton will assume responsibility for submitting the reportable event(s) to EMD Serono as well as ensuring that any local reporting requirements are completed in parallel.

Serious Adverse Events

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is another medically important event;
- Potential drug-induced liver injury (Hy's Law cases)

Exposure during Pregnancy or Breastfeeding (even if not associated with an AE)

Occupational exposure (even if not associated with an adverse event)

Contact information for submission of reportable events to EMD Serono:

Fax: +49 6151 72 6914

OR

E-mail: ICSR_CT_GPS@merckgroup.com Specifying: PROTOCOL Number and/or Title, EMD Serono assigned Study Number SUBJECT Number, SITE Number/PI Name

7.0 TRIAL FLOW CHART

Trial Period:	Screening Phase	Treatment Cycles ^a								End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	To be repeated beyond 8 cycles				Discon	Safety Follow-up ^b	Follow Up Visits ^c	Survival Follow-Up
Scheduling Window (Days):	-21 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days from last dose (± 3 days)	Every 12 weeks post last dose (± 7 days)	Every 6 months (± 14 days) Or by phone
Administrative Procedures													
Informed Consent	X ^d												
Inclusion/Exclusion Criteria	X												
Demographics and Medical History	X												
Prior and Concomitant Medication Review	X ^e	X	X	X	X	X	X	X	X	X	X ^e		
Trial Treatment Administration		X ^f	X	X	X	X	X	X	X				
Subsequent Anticancer Therapy Status												X	X
Survival Status													X
Clinical Procedures/Assessments													
Adverse Events Monitoring	X	X	X	X	X	X	X	X	X	X	X ^g	X ^g	
Full Physical Examination ^h	X									X			
Directed Physical Examination ^h		X	X	X	X	X	X	X	X				
Vital Signs and Weight ⁱ	X	X	X	X	X	X	X	X	X	X			
12-Lead ECG	X												

Trial Period:	Screening Phase	Treatment Cycles ^a								End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	To be repeated beyond 8 cycles				Discon	Safety Follow-up ^b	Follow Up Visits ^c	Survival Follow-Up
Scheduling Window (Days):	-21 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days from last dose (± 3 days)	Every 12 weeks post last dose (± 7 days)	Every 6 months (± 14 days) or by phone
ECOG Performance Status	X	X	X	X	X	X	X	X	X ^j	X			
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory													
CBC with Differential ^l	X ^k		X	X	X	X	X	X	X	X	X ^m		
Comprehensive Chemistry Panel ^l	X ^k		X	X	X	X	X	X	X	X	X ^m		
Urinalysis ^l	X ^k				X ⁿ				X ⁿ	X	X ^m		
FT4 and TSH ^l	X ^k				X				X	X	X ^m		
Testosterone ^l	X ^k				X ^o				X ^o	X ^o			
Tumor Marker Assessment (PSA) ^p	X	X	X	X	X	X	X	X	X	X		X	
Efficacy Measurements													
Tumor Imaging	X ^q						X ^p			X ^r		X ^s	
Tumor Tissue Collection/Correlative and Biomarker Studies													
Tumor Tissue Collection (Newly Obtained and Archival)	X ^t												

Trial Period:	Screening Phase	Treatment Cycles ^a								End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	To be repeated beyond 8 cycles				Discon	Safety Follow-up ^b	Follow Up Visits ^c	Survival Follow-Up
Scheduling Window (Days):	-21 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days from last dose (± 3 days)	Every 12 weeks post last dose (± 7 days)	Every 6 months (± 14 days) or by phone
Blood for Genetic Analyses		X ^u											
Tumor BROCA Testing ^v	X												
Blood for ctDNA (plasma) ^w	X						X			X			

- All treatment cycles are 2 weeks ± 3 days.
- If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up visit must occur before the start of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.
- Follow-up visits must occur every 12 weeks (84 days ± 7 days) from the date of last dose of study treatment for up to 1 year. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging (CT/MRI and bone scans) and PSA every 12 weeks until: 1) the start of new anti-cancer treatment, 2) documented disease progression, 3) death or 4) the end of the study, whichever occurs first.
- Written consent must be obtained prior to performing any protocol specified procedures. Results of a test performed prior to the subject signing consent are acceptable in lieu of new screening tests if they are a part of routine clinical management and performed within the specified timeframe.
- Prior medications: record all medications taken within 28 days prior to the first dose of trial treatment. Concomitant medications: all medications started during the trial and up to 30 days after last dose of trial treatment regardless of when the safety follow-up visit occurs. All medications related to reportable SAEs should be recorded.
- Trial treatment should begin on the day of treatment allocation or as close as possible to the date on which the subject is allocated.
- Record all AEs occurring up to 30 days after the last dose of trial treatment. SAEs must be recorded up to 90 days after the last dose of trial treatment or until the start of new anti-cancer treatment, whichever comes first. Treatment related SAEs must always be reported within 24 hours.
- A full physical exam will be performed at screening and at treatment discontinuation; all treatment visits will include a directed physical exam.
- Height will be measured at screening only.
- ECOG Performance Status will be performed on day 1 at every other cycle and at treatment discontinuation.
- Laboratory procedures at screening are to be performed within 10 days prior to the first dose of trial treatment.
- After Cycle 1, pre-infusion laboratory procedures may be conducted up to 72 hours pre-infusion, labs are specified in section 8.7; table 5.
- Unresolved abnormal lab results associated with drug-related AEs should be followed until resolution.
- Urinalysis and thyroid function testing are done at screening, every 4 cycles or 8 weeks, treatment discontinuation, and the safety follow-up visit.
- Testosterone will be done at screening, every fourth cycle (Cycles 4, 8, 12,...) and at treatment discontinuation
- Imaging assessments (CT/MRI and bone scans) and PSA should be performed every 12 weeks, at treatment discontinuation and during follow-up. The timing of these assessments should not be adjusted for dose delays or cycle starts.
- The initial tumor imaging will be performed within 28 days prior to the first dose of trial treatment. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the first dose of trial treatment.
- If a scan was obtained within 4 weeks prior to treatment discontinuation, then another scan at discontinuation is not mandatory. Radiological evaluation should be repeated

- at treatment discontinuation in subjects discontinuing without confirmed disease progression (date of discontinuation \pm 4 weeks).
- s. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging (CT/MRI and bone scans) and PSA (every 12 weeks from the date of last dose of study treatment) until: 1) the start of new anti-cancer treatment, 2) documented disease progression, 3) death or 4) the end of the study, whichever occurs first.
 - t. Baseline tumor tissue for biomarker analysis from an archival tissue sample and/or newly obtained core or excisional biopsy from non-radiated metastasis may be obtained for correlative studies for responders. Refer to Section 9.
 - u. Blood will be collected to obtain genetic analyses at time of initial treatment and run on patients responding
 - v. Tumor BROCA testing will be performed on all feasible samples if patient agreeable to additional testing. This is not a requirement to participate in this study.
 - w. Blood for cfDNA will be obtained every 3 months IF feasible for Guardant 360 testing on responders, once confirmed

8.0 DETAILED STUDY DESIGN

8.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if additional information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

8.2 Inclusion and Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

8.3 Assignment of Treatment Number

All eligible subjects will receive a treatment number. The treatment number identifies the subject for all procedures occurring after treatment allocation. Once a treatment number is assigned to a subject, it can never be re-assigned to another subject. Treatment numbers will begin with 001. If a patient is a screen failure, they will be assigned the next number in sequence, and that number will not be replaced.

A single subject cannot be assigned more than 1 treatment number.

8.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will include all active conditions and any conditions diagnosed within the prior 10 years that are considered clinically significant by the Investigator. Details pertaining to the subject's prostate cancer diagnosis will be recorded separately and not listed as medical history.

8.4.1 History of Prostate Cancer

The investigator or qualified designee will obtain information regarding the subject's prostate cancer. This information will include but is not limited to the presentation at primary diagnosis, date and stage at primary diagnosis, date of and stage at most recent recurrence, and location of metastases at screening (if applicable).

8.4.2 Prior Treatment for Prostate Cancer

The investigator or qualified designee will review and report all prior treatments to prostate cancer including systemic treatments, radiation, and surgeries.

8.5 Prior and Concomitant Medications

8.5.1 Prior Medications

The investigator or qualified designee will review and record prior medication taken by the subject within 28 days prior to the first dose of trial treatment.

8.5.2 Concomitant Medications

The investigator or qualified designee will record medications taken by the subject during the trial up to 30 days after the last dose of trial treatment. All medications related to reportable SAEs should be recorded.

8.6 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-cancer therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up visit must occur before the start of the new therapy. Once new anti-cancer therapy has been initiated, the subject will move into survival follow-up.

8.7 Clinical Procedures/Assessment

8.7.1 Adverse Event Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0 (see Appendix C). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with avelumab exposure should be evaluated to determine if they are events with potential immunologic etiology. See Section 6.3 Table 3 regarding the identification, evaluation, and management of AEs of a potential immunological etiology.

Please refer to Section 6.11 for detailed information regarding the assessment and recording of AEs within 24hours.

8.7.2 Physical Exam

8.7.2.1 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period and at treatment discontinuation. Clinically significant abnormal findings at screening should be recorded as medical history. New clinically significant abnormal findings at treatment discontinuation should be recorded as AEs.

8.7.2.2 Directed Physical Exam

The investigator or qualified designee will perform a directed physical exam, as clinically indicated, prior to dosing on Day 1 of each treatment cycle. New clinically significant abnormal findings should be recorded as AEs.

8.7.2.3 Vital Signs

The investigator or qualified designee will assess vital signs at screening, prior to dosing on Day 1 of each treatment cycle and at treatment discontinuation. Vital signs include temperature, heart rate, respiratory rate, weight and blood pressure. Height will be measured at screening only

8.7.3 12-Lead ECG

A standard 12-lead ECG will be performed once at the screening visit using local standard procedures. Clinically significant abnormal findings should be recorded as medical history.

8.7.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG Performance Status at screening and prior to dosing on Day 1 of each treatment cycle, and at treatment discontinuation. This scale can be found for reference in appendix D.

8.7.5 TUMOR IMAGING AND ASSESSMENT OF DISEASE

Tumor imaging should be acquired by computed tomography (CT, strongly preferred) and radionuclide bone scan. Magnetic resonance imaging (MRI) should be used where CT is contraindicated or for imaging in the brain. The same imaging technique regarding modality and use of contrast should be used in a subject throughout the trial to optimize the visualization of existing and new tumor burden. Tumor imaging by both CT (or MRI) and radionuclide bone scan is required at every scheduled imaging time point.

8.7.5.1 Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 28 days prior to the date of first dose of trial treatment. Tumor imaging by both CT (or MRI) and radionuclide bone scan is required at screening.

Scans performed as part of routine clinical management are acceptable for use as the screening scans if they are of diagnostic quality, performed within 28 days prior to the date of first dose of trial treatment.

At screening, all lesions seen by CT (or MRI) and radionuclide bone scan will be documented. In determining response to treatment or progression, investigators must evaluate all target and non-target lesions and search for new lesions at each imaging time point.

8.7.5.2 Tumor Imaging During Trial

On study imaging assessments must be performed every 12 weeks (± 7 days). Imaging timing should follow calendar days from date of allocation and should not be adjusted for delays in cycle starts.

1. RESPONSE

Per RECIST 1.1, response should be confirmed by a repeat radiographic assessment not less than 4 weeks from the date response was first documented. The scan for confirmation of response may be performed ≥ 4 weeks after the first indication of response or at the next scheduled scan, whichever is clinically indicated. Subjects who obtain a repeat scan do not need to undergo the next scheduled imaging if it is < 4 weeks after the confirmation scan. Subjects will return to their regular imaging schedule starting with the next time point.

2. PROGRESSION

Radiographic progression for soft tissue lesions will be determined according to RECIST 1.1 (see appendix A). Disease progression in soft tissue lesions should be confirmed by the site ≥ 4 weeks after the first radiologic evidence of PD. Subjects who have unconfirmed disease progression and are clinically stable may continue treatment at the discretion of the investigator until progression is confirmed by the site. Subjects who obtain a repeat scan do not need to undergo the next scheduled imaging if it is < 4 weeks after the confirmation scan. Subjects will return to their regular imaging schedule starting with the

next time point. Subjects who have confirmed disease progression, as assessed by the site, will discontinue treatment.

Radiographic progression for bone lesions will be determined as described in the consensus guidelines of the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) (see appendix B).

If a subject with confirmed radiographic progression is clinically stable or clinically improved, and there is no further increase in the tumor dimensions at the confirmatory scan, an exception may be considered to continue treatment.

Imaging should continue to be performed until documented disease progression, the start of new anti-cancer treatment, withdrawal of consent or death, whichever occurs first.

Table 4. Imaging and Treatment after 1st Radiologic Evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
1 st radiologic evidence of PD	Repeat imaging at ≥ 4 weeks to confirm PD (soft-tissue progression) Repeat bone scan at ≥ 6 weeks to confirm PD (bone progression)	May continue study treatment at the Investigator's discretion while awaiting confirmatory scan	Repeat imaging at ≥ 4 weeks to confirm PD if possible (soft-tissue progression) Repeat bone scan at ≥ 6 weeks to confirm PD if possible (bone progression)	Discontinue treatment
Repeat scan confirms PD	No additional imaging required	Discontinue treatment	No additional imaging required	N/A
Repeat scan shows SD, PR or CR	Continue regularly scheduled imaging assessments every 12 weeks	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments every 12 weeks	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion

*clinically stable subjects should have repeat imaging and may stay on treatment at the discretion of the investigator

8.7.6 End of Treatment and Follow-up Tumor Imaging

In subjects who discontinue trial treatment, tumor imaging should be performed at the time of treatment discontinuation (\pm 4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation another scan at treatment discontinuation isn't mandatory. In subjects who discontinue trial treatment due to documented disease progression, this is the final required tumor imaging.

In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule the subject was on during treatment (every 12 weeks after the date of last dose) until: 1) the start of new anti-cancer treatment, 2) disease progression, 3) death or 4) the end of the study, whichever occurs first.

8.7.7 Treatment Beyond Progression

When feasible, subjects should not be discontinued until progression is confirmed by the local site investigator/radiology assessment. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy and then experience subsequent disease response and/or may have radiographic progression that is not clinically significant. Subjects that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation of PD.

In subjects who have shown initial evidence of radiological PD by RECIST 1.1, it is at the discretion of the PI whether to continue a subject on study treatment until repeat imaging is obtained. This clinical judgment decision by the site investigator should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects who are clinically stable may continue receiving study therapy.

Clinically stable subjects should also have at the confirmatory scan no further increase in the target lesions, no unequivocal increase in non-target lesions and no additional new lesions develop (non-worsening PD) to continue study treatment.

8.7.8 Tumor Marker Assessment (PSA)

The initial Prostate-Specific Antigen (PSA) biomarker assessment at screening must be performed within 10 days prior to the date of initiation of treatment.

On study PSA biomarker assessments must be performed every 2 weeks from the date of initiation of treatment and for as long as subject remains on treatment. PSA should be measured on day 1 of each cycle regardless of cycle delays.

In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by PSA biomarker assessments using the same schedule the subject was on during treatment (every 12 weeks from the date of last dose) until: 1) the start of new anti-cancer treatment, 2) disease progression, 3) death or 4) the end of the study, whichever occurs first

PSA progression will be defined as follows:

1. For those with no PSA decrease from baseline, a rise in PSA of 25% or more (of at least 2ng/mL or more) construes progression at a time point 6 or more weeks after therapy initiation (and/or at least 3 treatment administrations of avelumab)

For those with a PSA decrease after starting therapy, the PSA should rise 25% from the nadir (at least 2 ng/mL increase) with a confirmed increase 2 or more weeks later. **8.7.9 Sample testing for Ancillary studies**

8.7.9.1 Tissue for BROCA testing

If tissue samples available, testing for BROCA will be performed in coordination with University of Washington Genetics and Solid Tumors Laboratory on all patients with response to treatment. If no tissue available, additional biopsy of new/viable progressing tumor will be considered but is not a requirement for study enrollment.

8.7.9.2 ctDNA Sample testing for ancillary studies

ctDNA will be obtained at time of enrollment or within 4 weeks of screening visit and then every 12 weeks +/- 2 weeks. These samples will be stored on site as designated. Guardant 360 test will be performed with each sample on those found to be responding to treatment at 8-12 weeks.

8.7.10 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Table 5. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Platelet Count	Alanine Aminotransferase (ALT)	Protein	Free Thyroxine (FT4)
WBC (Total and Differential)	Aspartate Aminotransferase (AST)	Specific Gravity	Thyroid Stimulating Hormone (TSH)
Red Blood Cell Count	Lactate Dehydrogenase (LDH)	Microscopic Exam (If abnormal results are noted)	Blood for Genetic Analysis
Absolute Neutrophil Count	Carbon Dioxide ^a (CO ₂ or bicarbonate)		Testosterone
Absolute Lymphocyte Count	Calcium		Prostate-Specific Antigen (PSA)
	Chloride		BROCA testing (tissue)
	Glucose		ctDNA testing
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin (If total)		
	Total protein		
	Blood Urea Nitrogen		

	Creatinine		
	Creatinine		
	Creatinine		
	Creatinine		

After Cycle 1, pre-dose laboratory procedures may be conducted up to 72 hours prior to dosing. Results of scheduled laboratory tests must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment. Any results found to be clinically unacceptable may be repeated, abnormal lab values should be recorded as AE and treated if necessary, and followed until resolution.

8.8 Withdrawal/Discontinuation

Subjects who discontinue/withdraw from treatment prior to completion of the treatment regimen should be encouraged to continue to be followed for all remaining study visits.

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the End-of-Treatment visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 6.7 – Safety Monitoring.

8.9 Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

8.10 Post-Treatment

Subjects will be required to return to clinic approximately 30 days after the last dose of trial drug for the post-treatment visit. If the post-treatment visit occurs less than 30 days after the last dose of trial drug, a subsequent follow-up phone call should be made at 30 days post the last dose of trial drug to determine if any adverse events have occurred since the post-trial clinic visit.

8.10.1 Follow Up

After the 30-day safety follow up, patients will enter the follow up phase of the study. Follow-up visits must occur every 12 weeks (84 days \pm 7 days) from the date of last dose of study treatment for up to 1 year. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging (CT/MRI and bone scans) and PSA every 12 weeks until: 1) the start of new anti-cancer treatment, 2) documented disease progression, 3) death or 4) the end of the

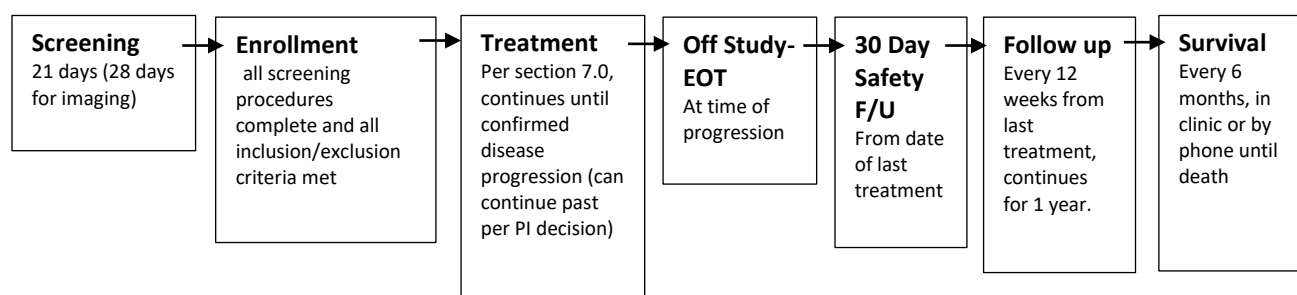
study, whichever occurs first. Once that patient experiences progression, they move into typical follow up procedures which will occur every 12 weeks.

8.10.2 Survival Follow-up

After completion of one year of follow up, all patients will move into survival follow up, where they will be contacted in clinic, or by telephone, every 6 months (+/- 14 days) to assess subsequent cancer therapies and survival. This phase will continue until death, withdrawal of consent or end of study, whichever comes last.

8.11 Simple Study Phase Flow Diagram

Figure 2:



9.0 STATISTICAL JUSTIFICATION

9.1 Statistical Analysis Plan Summary

The primary efficacy variable is the proportion of successes, where success for a patient is a decrease in PSA of at least 50% from baseline and/or a radiographic response using RECIST 1.1 criteria. In the pre-expansion cohort, further development would not be indicated if certain thresholds are not met on at least two occasions. We expect that the response rate is at least 10-20% in the general population based on prior PD-1 inhibitor data, and potentially higher in the AA population. Of note, we anticipate the majority of responses will occur within 8-12 weeks of treatment initiation.

This trial will test the hypothesis using a two-stage minimax plan with a desirable response probability of $\geq 20\%$ in AA with a goal of 80% power and an undesirable response probability of $\leq 5\%$ with an $\alpha = 0.05$.

The pre-expansion cohort will enroll 13 patients to be treated with the trial drug for an anticipated 8-12 weeks. This study will be terminated if 0 subjects respond and further study will be deemed of little interest. If there are 1 or more responses in the pre-expansion cohort, the study will be expanded to a second stage, with a total of 27 evaluable African American patients enrolled. If the total number responding ≤ 3 , that cohort will be terminated given further study will be deemed of little interest. Evaluable patients are all those that have at least one PSA value

or radiographic assessment 8 or more weeks post initiation of treatment with avelumab; patients that progress or die earlier than 8 weeks are considered non-responders.

Using this design, if the trial drug is ineffective, there will be a 0.0416 probability of concluding that it is effective (the target value is 0.050). If the trial drug is effective at the proposed response rate of at least 20%, there is a 0.1989 probability of concluding that it is not effective (the target value is 0.200).

Study Design Overview	Phase II Trial of Avelumab plus 2 nd -generation ADT in AA Subjects with mCRPC
Treatment Assignment	All subjects will receive avelumab 10mg/kg mg administered intravenously (IV) every 2 weeks (Q2W).
Statistical Justification	No response in 13 patients in pre-expansion cohort excludes the possibility of a clinically relevant response rate of $\geq 20\%$.
Primary Endpoint(s)	PSA response $\geq 50\%$ at ≥ 8 weeks
Secondary Endpoints	PSA progression-free survival using PCWG3 criteria; radiographic PFS by PCWG3 criteria, OS, and safety as determined by CTCAE v4.0 criteria
Correlative studies	We propose cfDNA, germline, and BROCA testing of tumors when feasible using either non-radiated primary or metastatic lesions for all responders.

9.2 Primary Endpoint

The primary endpoint is a PSA response at 8 weeks or greater from starting study treatment and with a minimum of 3 treatments administered.

- A PSA response is defined as a $\geq 50\%$ PSA decline at 8 weeks or greater from the time of starting study treatment. The two-stage minimax design of the study will be utilized to determine whether further investigation of the study drug is warranted.

9.3 Secondary Endpoints

The secondary endpoints are:

- PSA progression-free survival (pPFS) defined as the time from enrollment until PSA progression by PCWG3 or death, whichever occurs earlier. Subjects without pPFS at the time of data cut-off will be censored at the date of last adequate cancer assessment. PSA progression-free survival will be reported using Kaplan-Meier estimates, with 95% CI for median time-to-event.

- Radiographic progression-free survival (rPFS) defined as the time from enrollment until radiographic progression by PCWG3 or death, whichever occurs earlier. Subjects without rPFS at the time of data cut-off will be censored at the date of last known to be alive. Radiographic progression-free survival will be reported using Kaplan-Meier estimates, with 95% CI for median time-to-event.
- Overall survival (OS) defined as the time from enrollment until death on study. Subjects who are alive at the time of data cut-off will be censored at the date of last known to be alive. OS will be reported using Kaplan-Meier estimates, with 95% CI for median time-to-event.
- Safety will be summarized by nature, severity, and frequency utilizing CTCAE version 4.03.

10.0 REFERENCES

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11. Appendices

A. RECIST v1.1

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

As published in the European Journal of Cancer [12].

B. Prostate Cancer Clinical Trials Working Group 3

PCWG3 will be used in this study to assess PSA response.

As published in Journal of Clinical Oncology (13)

C. CTCAE v.0

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version .0 will be utilized for adverse event reporting.

(<https://evs.nci.nih.gov/ftp1/CTCAE/About.html>)

D. ECOG Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655

<http://ecog-acrin.org/resources/ecog-performance-status>

E. Abiraterone

Dosing and dose modifications will be up to prescriber's discretion. Monitoring and modifications shall follow standard manufacturer's recommendations which can be found at the following:

<https://www.zytiga.com/shared/product/zytiga/zytiga-prescribing-information.pdf>

F. Enzalutamide

Dosing and dose modifications will be up to prescriber's discretion. Monitoring and modifications shall follow standard manufacturer's recommendations which can be found at the following:

<https://www.astellas.us/docs/us/12A005-ENZ-WPI.pdf>

G. Apalutamide

This section will be updated upon approval of commercial drug

H. Darolutamide

This section will be updated upon approval of commercial drug

I. Avelumab Pharmacy Manual

Product Information			
Product name:	Avelumab (MSB0010718C)	Dosage/Strength:	20mg/ml
Purpose:	Investigator Sponsored Study	Administration Route:	IV

<p>Pharmacy Manual Investigator Sponsored Study Use of Avelumab</p>

PDL-1 inhibition with Avelumab and concurrent second-generation ADT in African Americans with castrate-resistant metastatic prostate cancer.

MS100070-0011

PURPOSE OF THE PHARMACY MANUAL	
The Pharmacy Manual summarizes the information collected during the Clinical Administration Study ¹ in order to support the preparation of the investigational medicinal product for use in an Investigator Sponsored Study setting by giving indication on handling instruction, approved ancillaries and in use stability.	

1.0	DESCRIPTION OF THE INVESTIGATIONAL MEDICINAL PRODUCT (IMP)
1.1	<p>General information:</p> <p>Avelumab drug product is a fully human antibody of the IgG1 isotype that specifically targets and blocks the ligand (PD-L1) for PD-1.</p> <p>Merck KGaA will package and distribute the IMP to sites via their distribution vendor - Fisher Clinical Services. The IMP will be shipped in transport cool containers (2°C to 8°C) that are monitored with temperature control devices.</p>
1.2	<p>Pharmaceutical formulation:</p> <p>Avelumab is a sterile solution intended for intravenous (IV) infusion.</p>
1.3	<p>Description of the formulation:</p> <p>The investigational product avelumab is a sterile, clear, colorless and non-pyrogenic solution for intravenous infusion.</p> <p>It is presented in Type I glass vials filled with 10 mL of liquid (200 mg/vial), closed with a rubber septum and sealed with an aluminum flip off seal.</p> <p>Each single-use vial contains 200 mg of avelumab, formulated as a 20 mg/mL preservative-free acetate buffered solution at pH 5.2 in presence of Polysorbate 20 and Mannitol.</p> <p>This product requires further dilution prior to IV infusion.</p>
1.4	<p>Description of the infusion solution:</p> <p>Avelumab infusion solution should be prepared by dilution in 0.9% Sodium Chloride (Normal Saline) (or in 0.45% Sodium Chloride, only if the first option is not applicable). The verified avelumab concentration range in the infusion solution is 0.016 mg/mL to 8 mg/mL.</p>

¹ Study N° 60259: Clinical Administration Study of Anti PDL1 200mg/vial presentation for PhII/III

2.0	DETERMINATION OF SUBJECT DOSE (see Annex 4 for worksheet)
	<p>Dosing calculation:</p> <p>The required dose (mg) is based on the patient's bodyweight (kg) at each visit, unless otherwise indicated in the study protocol.</p> <p><u>Step 1: Calculation of Dose</u></p> <p>Equation 1: Required dose (mg) = 10 (mg/kg) x patient weight (kg)</p> <p>For example: For a patient weighing 75 kg: Required dose (mg) = 10 mg/kg x 75 kg = 750 mg</p> <p><u>Step 2: Calculation of Number of Vials</u></p> <p>Calculate the required number of avelumab drug product (DP) vials. Round up to the next whole number of vials.</p> <p>Equation 2: # of assigned vials for DP = $\frac{\text{Required dose from Equation 1 (mg)}}{200 \text{ (mg/vial)}}$</p> <p>For example: # of assigned vials for DP = $\frac{750 \text{ mg}}{200 \text{ mg/vial}} = 3.75 \text{ vials}$</p> <p>Rounded up to the next whole number = 4 vials</p>

3.0	PREPARATION FOR USE
3.1	<p>General Instructions:</p> <p>To prepare the dilutions, subsequent preparation steps must be accomplished by adequate trained personnel to guarantee the sterility of the product to be injected.</p> <p>Preferred method is to prepare the solution under laminar flow box using aseptic techniques. If a laminar flow box is unavailable, alternative procedures and aseptic handling techniques in place that prevent microbiological contamination may be used.</p> <p>Only the necessary materials should be present in the working area during each preparation step.</p> <p>Only clinical site personnel who are appropriately trained on the procedure detailed in this document may perform the preparation and administration procedures specified in this manual. Clinical site personnel involved in these procedures must comply with all applicable regulations and standards.</p> <p><i>Utilize local site procedures as appropriate.</i></p> <p>Safety Precautions:</p> <p><u>Handling Information:</u> Recommendation in the Safety Data Sheet (SDS) should be followed. The SDS will be provided separately.</p> <p><u>Safety Equipment Used:</u> Appropriate gowning and footwear as per local site procedures.</p>
3.2	<p><u>Calculation of Volume of Avelumab and Normal Saline Required</u></p> <p>Based on a total infusion volume of 250 mL, calculate the volume of avelumab and Normal Saline required to prepare the infusion bag:</p> <p>Equation 3:</p> $\text{Volume of avelumab (mL)} = \frac{\text{Required dose from Equation 1 (mg)}}{20 \frac{\text{mg}}{\text{mL}}}$ <p>Equation 4:</p> $\text{Volume of Normal Saline (mL)} = 250 \text{ mL} - \text{Volume of avelumab (from Equation 3)}$ <p>For example:</p> <p>Using the same examples as above:</p> $\text{Volume of avelumab (mL)} = \frac{750 \text{ mg}}{20 \frac{\text{mg}}{\text{mL}}} = 37.5 \text{ mL (Round to the nearest tenth place \#.X)}$ $\text{Volume of Normal Saline (mL)} = 250 \text{ mL} - 37.5 \text{ mL} = 212.5 \text{ mL (Round to the nearest whole number)}$

<p>3.3</p>	<p><u>Preparation of Dosing Solution</u></p> <ol style="list-style-type: none"> Ensure that all materials (see Annex 2 for list of approved ancillary materials) and equipment required are available before starting the dose preparation Remove the vial(s) required for the dose to be prepared and allow the vial(s) to reach room temperature prior to preparing dose for 30 (+20) minutes Gently invert the vial(s) several times before use. Do NOT shake or agitate vigorously. Follow the preparation steps below according to the type of IV infusion bag used for dose preparation. Refer to Annex 3 for additional examples. <p>If using an empty IV infusion bag:</p> <ol style="list-style-type: none"> Add the volume of Normal Saline* calculated in Equation 4 to the appropriate sized empty bag using appropriately sized syringes with 18-22G needle(s) (preferably 18G needles). Add the volume of avelumab (mL) calculated in Equation 3 to the bag containing Normal Saline* using a new appropriately sized syringe(s) with 18-22G needle(s) (preferably 18G needles). <p>If using a pre-filled Normal Saline* IV infusion bag[§]:</p> <ol style="list-style-type: none"> Remove a volume corresponding to the volume of avelumab (mL) calculated in Equation 3 from the pre-filled bag containing Normal Saline using an appropriately sized syringe with 18-22G needles (preferably 18G needles). Add the calculated volume of avelumab (mL) from Equation 3 to the pre-filled bag containing Normal Saline* using a new appropriately sized syringe with an 18-22G needle(s) (preferably 18G needles). <p><i>* Note: The standard solution to be used for the dilution is 0.9% saline solution. Only if this solution is not available, 0.45% saline solution may be used.</i></p> <p><i>§ Note: if the bag is pre-filled with more than 250 mL (for example, 500 mL), discard the excess volume of saline solution. This option should be considered only if 250 mL bags are not available.</i></p> <ol style="list-style-type: none"> Gently invert the prepared IV bag 10 times to mix. Do NOT shake. Attach appropriate label to the IV infusion bag. <p>For any site whose local/institutional guidelines require the use of an over-fill infusion preparation procedure, the local/institutional guidelines may be used provided the following requirements are fulfilled:</p> <ul style="list-style-type: none"> An infusion bag large enough to hold the final volume of prepared product is used The dose calculation performed to determine the concentration of avelumab drug product is to be based on the total volume of the preparation specified in this manual. The over-fill has to be calculated using the same concentration A copy of the protocol used for over-fill infusion preparation will be maintained in the pharmacy records <p>Document the actual dose administered and amount of required over-fill in the pharmacy records.</p>
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4.0	ADMINISTRATION INSTRUCTIONS
	<p>The administration must be performed by adequately trained personnel. Prior to dosing the subject, adhere to normal standard of care and aseptic techniques.</p> <p>The prepared avelumab dosing solution for infusion is connected to the infusion set equipped with a 0.2 micron PES (or PSU but only if PES membrane is not available) in-line filter and an appropriate gauge standard venous catheter for the subject. Alternatively, a permanent venous catheter or implantable port may be used. Prior to infusion, prime the assembly with the dosing solution.</p> <p>Set the infusion pump to deliver the entire infusion volume over 1 hour (-10/+20 minutes). A constant infusion rate is achieved by using a microprocessor-controlled infusion pump.</p> <p>Immediately following the infusion of avelumab, it is recommended (but not mandatory) to conduct a normal saline flush using the same tubing and 25-100 mL normal saline infused at the same rate to clear the infusion set of residual drug.</p> <p>Document administration details in the pharmacy records.</p>

5.0	STORAGE AND IN-USE STABILITY
	<p><u>Drug Product Vials</u></p> <p>Storage conditions:</p> <p>MSB0010718C drug product must be stored in the original packaging at refrigerated conditions (2- 8°C, 36-46°F) until use with a temperature log maintained daily. The storage condition is based on data from ongoing long term stability studies with avelumab.</p> <p>Avelumab drug product stored at room temperature (15-25°C, 59-77°F) or higher temperatures for extended periods of time might be subject to degradation.</p> <p>Avelumab drug product must not be frozen.</p> <p>In the event of a temperature excursion:</p> <ul style="list-style-type: none"> • Inform Fisher Clinical Services immediately by sending a Temperature Excursion Form (provided separately) to _AvelumabTemperatureExcursion@thermofisher.com <p>And</p> <ul style="list-style-type: none"> • Quarantine vials until further approval for use is received

Handling conditions:

Prior to the preparation of the dilution for final infusion, allow each vial to equilibrate to room temperature (15-25°C, 59-77°F) preferably for 30-50 min.

Rough shaking of the solution must be avoided. Addition of other medication to the infusion containers containing avelumab must be avoided.

Retention of Drug Product Vials:

All opened vials (full, partially full, and empty) may be destroyed at the site by the appropriate site personnel (e.g., pharmacist, study nurse/coordinator) following local environmental requirements and institutional policies. All destruction must be fully documented at the time of destruction on the investigational product accountability log, or equivalent document at the time of destruction.

If opened vials are not destroyed immediately following drug preparation, opened vials must be stored in sealed, clear plastic bags until destruction.

All unopened vials must be destroyed at the end of the treatment period unless Merck KGaA provides separate instructions for return.

Prepared Dosing Solution ready to be injected

Avelumab drug product must be diluted with a Normal Saline solution (Sodium Chloride for injection).

Immediate administration of the prepared dosing solution is preferred.

In case prepared dosing solution cannot be administered immediately after preparation, the acceptable holding time is: no more than 8 hours at room temperature (15-25°C, 59-77°F), including infusion time, **or** no more than 24 hours under refrigerated conditions (2-8°C, 36-46°F), including infusion time.

If stored under refrigerated conditions, allow each bag to equilibrate to room temperature (15-25°C, 59-77°F), preferably for one hour before administration.

If not used following the indications reported in this Pharmacy Manual, in-use storage times and conditions prior to administration are the responsibility of the user.

Vehicular Transport of Prepared Dosing Solution ready to be injected

Vehicular transport of the prepared avelumab diluted solution from a compounding facility to a clinical centre is not recommended: it could cause a non-controlled rough shaking of the solution, that can induce aggregation of the medication.

In case remote preparation of the dosing solution and transport by vehicle cannot be avoided, certain requirements must be followed:

- Transportation transit time of prepared infusion bag cannot be more than 22 hours,
- Dosing solution must be controlled at refrigerated conditions (2- 8°C, 36-46°F) during transport. The time required to reach the target temperature (from 2-8°C to 25°C) may not be more than 3 hours
- Dosing solution must be allowed to equilibrate to room temperature (15-25°C, 59-77°F), prior to administration, preferably for one hour before administration

- Transportation documentation, including transit time and temperature control, must be maintained in the pharmacy files.

Retention of supplies:

Normal saline solution may be disposed of according to local site procedures. Other items used in the dose preparation and administration should be disposed of according to local site procedures.

6.0	HISTORY OF CHANGES		
Document History			
Version	Reason for Versioning	Date	
V 1.0	Issuing of new document (based on MOP v4.0)	10 Jun 2016	
V 2.0	Updated to align with v6 of the avelumab Manual of Preparation: MSB0010718C substituted with avelumab throughout document Par 2.0: update sentence linked to “dosing calculation” Par.5.0: Change in the holding time conditions for prepared solution for dosing based on new data from microbial challenge study. Update sentence linked to the “prepared dosing solution ready to be injected”. Introduction of instruction for vehicular transport of prepared dosing solution ready to be injected	09 May 2017	

ANNEX 1

Glossary	
DP	Drug Product
EVA	Ethylene Vinyl Acetate
IV	Intravenous
PB	Polybutadiene
PE	Polyethylene
PES	Polyethersulfone
PP	Polypropylene
PSU	Polysulfone
PUR	Polyurethane
PVC	Polyvinylchloride

ANNEX 2

Approved materials

All ancillaries made of the materials included in the following list, DEHP, latex free, FDA approved can be used.

The use of 0.2 µm PES (polyethersulfone) in-line filters is mandatory. Alternatively, 0.2 µm PSU (polysulfone) in-line filters can be used (PES to be preferred).

List of approved materials:

acronym	material
EVA	ethylene vinyl acetate
PB	polybutadiene
PE	polyethylene
PES	polyethersulfone
PP	polypropylene
PSU	polysulfone
PUR	polyurethane
PVC	polyvinyl chloride
Silicone	silicone
Titanium	titanium

ANNEX 3

Examples for target dose calculation (pre-filled 250 mL bags)*

Dose level (mg/kg)	Patient's bodyweight (kg)	Target dose for administration (mg)	Volume of 0.9% sodium chloride solution to be withdrawn from infusion bag (mL)	Volume of avelumab drug product to be added to the infusion bag (mL)	Final nominal volume for administration (mL)	Final nominal avelumab concentration in the infusion solution (mg/mL)	Number of DP vials required for preparation
10	40	400	20	20	250	1.6	2
10	120	1200	60	60	250	4.8	6
10	200	2000	100	100	250	8.0	10
0.1	40	4	0.2	0.2	250	0.0016	1

* Round to the nearest tenth place for DP volume to be added

Examples for target dose calculation (empty 250 mL bags)*

Dose level (mg/kg)	Patient's bodyweight (kg)	Target dose for administration (mg)	Volume of 0.9% sodium chloride solution to be added to the empty infusion bag (mL)	Volume of avelumab drug product to be added to the infusion bag (mL)	Final nominal volume for administration (mL)	Final nominal avelumab concentration in the infusion solution (mg/mL)	Number of DP vials required for preparation
10	40	400	230	20	250	1.6	2
10	120	1200	190	60	250	4.8	6
10	200	2000	150	100	250	8.0	10
0.1	40	4	249.8	0.2	250	0.0016	1

* Round to the nearest tenth place for DP volume to be added

ANNEX 4

MSB0010718C (Avelumab) Intravenous Administration – Investigator Sponsored Study

The appropriate details should be filled in here prior to dose preparation (or documented otherwise in the pharmacy files).

Patient Name: _____ Patient Date of Birth: _____ Patient Weight: _____ kg

Equation 1: Dose (mg) = $\frac{\text{Subject Weight (kg)}}{\text{Dose (mg)}} \times \text{mg/kg} = \text{Dose (mg)}$ mg

Equation 2: Number of avelumab Vials = $\frac{\text{Dose (mg)}}{200 \text{ mg/vial}} = \text{vial(s)}$

Equation 3: Volume of avelumab (mL) = $\frac{\text{Dose (mg)}}{20 \text{ mg/mL}} = \text{mL}$ (Round to the nearest tenth place)

Equation 4: Volume of Normal Saline (mL) = 250 mL - $\frac{\text{(from Equation 3)}}{\text{(Round to the nearest whole number)}} = \text{mL}$

Date of dose preparation: _____ (dd-mmm-yyyy)

Time at start of dose preparation: _____ (hh:mm) ☐ AM ☐ PM

Expiry Date and Time of Prepared Dose:

Expiry Date: _____ (dd-mmm-yyyy) Expiry Time: _____ (hh:mm) ☐ AM ☐ PM

The expiry time is 24 hours from the time the vials were removed from the refrigerator and allowed to reach room temperature

Calculation by (Print Name and initials): _____ Date: _____ (dd-mmm-yyyy)

Verified by (Print Name and initials): _____ Date: _____ (dd-mmm-yyyy)

Instructions for Preparation	Data
Indicated type and volume of bag used for dose preparation	<input type="checkbox"/> Empty: _____ mL Bag <input type="checkbox"/> Pre-filled: 0.9% NaCl _____ mL Bag
Volume of Normal Saline • Removed from a pre-filled bag (volume from Equation 3), OR • Added to an empty IV bag (volume from Equation 4	_____ mL <input type="checkbox"/> Removed <input type="checkbox"/> Added
Volume of avelumab added to prepared IV bag (from Equation 3)	_____ mL

Prepared by (Print Name and initials): _____ Date: _____ (dd-mmm-yyyy)

Verified by (Print Name and initials): _____ Date: _____ (dd-mmm-yyyy)

**Contact the responsible Treating Physician immediately to report any
dose preparation and administration deviations.**

Comments on dose preparation (record any deviations from Pharmacy Manual instructions; storage time, conditions, etc.):

J. Reporting, Assessment And Close Out of Temperature Excursion

REPORTING, ASSESSMENT AND CLOSE OUT OF TEMPERATURE EXCURSIONS - Avelumab Investigator Sponsored Study

Please complete Section 1, print, sign and scan, then send to: AvelumabTemperatureExcursion@thermofisher.com

Section 1 : Report (ALL excursions)	
Protocol N°/Trial No (as applicable/if applicable):	
Reporting Unit/Site/Depot/CMO: Site (include Site Name/Country as applicable / if applicable):	
Product (DS/DP/IMP/NIMP):	Batch N°:
Presentation:	Kit or patient N° (only IMP):
	Quantity of product affected:
Excursion occurred during: <input type="checkbox"/> Transport <input type="checkbox"/> Storage (CMO/Warehouse) <input type="checkbox"/> Storage (CMO/Depot) <input type="checkbox"/> Storage (CRO/ Site)	Apparent Cause: <input type="checkbox"/> Temperature deviation during storage/transport <input type="checkbox"/> Refrigerator, cold room, air-conditioning problems <input type="checkbox"/> Power failure <input type="checkbox"/> Other
Description of Excursion : Date : Temperature : Duration :	Documentation Attached <input type="checkbox"/> No, justification..... <input type="checkbox"/> Yes (please list)
Comments / Emergency Action Taken: Datalogger nr.:	
Person reporting the temperature excursion event Name/Function/Site: Signature : Date :	

Section 2 – ASSESSMENT (All excursions)		
Assessment Visual Appearance: <input type="checkbox"/> Container contents <input type="checkbox"/> Primary packaging <input type="checkbox"/> Secondary packaging		Data Assessment : <input type="checkbox"/> Complies with Transport and Storage Conditions <input type="checkbox"/> Data shows allowable excursion only
Result of Assessment by QP/Authorised/Delegate/QC: <input type="checkbox"/> Allowable Temperature Excursion – material can be confirmed for intended use, e.g. clinical use (Section 3 and 4 are not applicable) <input type="checkbox"/> Critical Temperature Excursion - requires Assessment/Investigation and decision by QP (See Page 2 of 2). EMD Serono Trackwise reference: (for critical deviations only, not relevant for Trial Sites/CROs)		
Comments:		
QP/Authorised/Delegated/QC: Name & Function : _____ Signature : _____ Date _____		

If assessed as allowable excursion, please send the close out to fax n° :

Section 3 – Investigation (Critical Temperature Excursions only)
EMD Serono Trackwise Deviation Reference (not relevant for site/CROs): Excursion Report Reference : Documentation Reviewed: Record of storage history: YES <input type="checkbox"/> NO <input type="checkbox"/> Data to support the deviation:

SECTION 4 - CLOSE OUT (Critical Temperature Excursions only)

Final Conclusion:

The product involved in the deviation can be used: YES ☐ NO ☐ (*Tick the relevant box*)

Comment:

Qualified Person Close Out:

Name :

Signature:

Date(data):

PDL-1 inhibition with Avelumab and concurrent second-generation ADT in African Americans with castrate-resistant metastatic prostate cancer.